EDITORIAL

Cerebral autoregulation in neurally mediated syncope: victim or executioner?

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Involvement of cerebral vasoconstriction confirms the complexity of the pathophysiology of neurally mediated syncope, and the need to adopt a comprehensive approach to the study of this problem

The pathophysiological mechanisms leading to neurally mediated syncope are complex and still not well defined. Even if the ''ventricular theory''[1] could represent one of the possible ways neurally mediated syncope develops, in many cases a clear increase in sympathetic activity, preceding the inhibitory reaction, is not always present.

On the other hand, it is clear that we cannot consider a single mechanism responsible for this form of syncope; we have to presume that it is the result of the interaction of many factors, which differ from patient to patient, and sometimes in the same individual from episode to episode.

In attempts to investigate these mechanisms, most studies have focused on cardiovascular changes induced by passive orthostatism, aiming to delineate the ''peripheral arch'' of the reflex—originating from carotid baroreceptors, cardiac mechanoreceptors, or other specific receptors, and releasing its effects on the heart and peripheral vascular system.

Starting in the early 1990s, thanks to the availability of non-invasive techniques to evaluate cerebral blood flow such as transcranial Doppler, attention shifted to the ''central arch'' of the reflex. The main question proposed was: are bradycardia and hypotension alone able to induce cerebral hypoperfusion which is finally responsible for loss of consciousness, or is an active cerebral vasoconstriction present?

CEREBRAL AUTOREGULATION

The central nervous system has specific autoregulatory mechanisms for cerebral circulation, confined in the arteriolar resistance vessels distal to the circle of Willis, which protect the brain from excessive changes in systemic arterial pressure.

Cerebral autoregulation is maintained by three different control pathways: myogenic, metabolic, and neurogenic. The first is based on the intrinsic ability of smooth muscular cells in arterioles to induce a vasoconstriction in response to a direct increase of cerebral blood pressure. In the second pathway, modifications of arteriolar resistance are induced by changes in local or systemic metabolism, such as adenosine, nitric oxide, carbon dioxide, or oxygen. Finally, the neurogenic mechanism is based on the presence of a rich innervation of cerebral vessels both by parasympathetic and sympathetic nerves. The latter, believed to be the more important, originates either from the brainstem or from sympathetic ganglions.

CEREBRAL VASOCONSTRICTION IN VASOVAGAL SYNCOPE

The results of studies conducted in this field are sometimes controversial. The peripheral hypotension should normally induce a reduction of cerebral vascular resistance to allow the maintenance of an adequate cerebral blood flow. However, the large majority of published papers demonstrate the presence of an active, paradoxical, cerebral vasoconstriction just before syncope, that could represent an important overwhelming phenomenon leading to cerebral hypoperfusion and therefore to loss of consciousness.

Grubb *et al*[2] first demonstrated the presence of this phenomenon in a group of subjects referred for unexplained syncope, just before tilt induced episodes, and considered this abnormal response to be an altered baroreceptor reaction. The same finding was subsequently confirmed by Levine *et al*[3] in a group of normal subjects, utilising a lower body negative pressure technique, in the moments before the onset of symptoms. However, the authors concluded that the magnitude of this response was not sufficient by itself to cause syncope. By the same technique, other authors provided similar findings in healthy subjects without previous episodes of loss of consciousness.[4]

More recently, the presence of a paradoxical cerebral vasoconstriction was also demonstrated by Lagi *et al*[5] in patients with vasovagal syncope. Nevertheless, he correlated this event to the presence of hypocapnia, induced by hyperventilation that occurred before symptoms.

In the following years other authors demonstrated the presence of a cerebral vasoconstriction before syncope, without confirming the presence of hypocapnia.[6]

Different hypotheses to explain this paradoxical increase of cerebral vascular resistance were later highlighted by Dan *et al*.[7] They showed that vasoconstriction preceded the reduction of systemic blood pressure, and therefore it cannot be considered a hypotension dependent reflex, but an independent, early event.

Only a few studies[8 9] have shown a normal working cerebral autoregulation in patients with tilt induced syncope, with a correct reduction of

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cerebral vascular resistance in response to a decrease in blood pressure.

CEREBRAL AUTOREGULATION IN CAROTID SINUS SYNDROME

Carotid sinus hypersensitivity is a frequent cause of syncope in elderly people, but its pathophysiology is still debated. Carotid sinus receptors, the autonomic centre of the brainstem, and the efferent limb of the reflex have all been incriminated. Recently, attention has been focused on two main hypotheses: an altered autonomic activity in the brainstem,[10] and a chronic denervation of the sternocleidomastoid muscle.[11]

In both vasovagal syncope and carotid sinus syndrome, the presence of an altered cerebral autoregulation has been proposed. However, the results presented until now are few and contrasting.

Some years ago Leftheriotis *et al*[12] compared the modifications of cerebral blood flow in patients with complete atrioventricular block and in patients with carotid sinus syndrome with vasodepressive and cardioinhibitory responses induced by carotid sinus massage. They demonstrated the presence of a normal cerebral autoregulation in both groups, with a normal decrease in cerebral vascular resistance in response to a reduction in blood pressure. This reduction, however, was preceded by a transient increase in patients with carotid sinus syndrome.

In this issue of *Heart*, Parry *et al*[13] present the results of a study that compares the changes of cerebral blood flow, by means of transcranial Doppler, in 17 patients with carotid sinus syndrome and in 11 healthy subjects, during lower body negative pressure. This test was adjusted to induce a significant hypotension, but not syncope. By means of this indirect method of baroreceptor stimulation the authors showed higher cerebral vascular resistance in the patient group, at baseline and during the test. The carbon dioxide values were monitored and the results stable, excluding the presence of a hyperventilation dependent hypocapnia.

The results of these two studies are not completely comparable. One important methodological difference is the use of a different test to stimulate carotid baroreceptors: carotid sinus massage in the first, lower body negative pressure in the second. Moreover, we have to consider that, in the first study, more severe reductions in blood pressure were induced (−40%), which were accompanied by loss of consciousness in two cases, while in the second study only a mild decrease was obtained.

The direct massage of carotid sinus mimics an increase in blood pressure that seems to induce, with a protective purpose, reflex peripheral vasodilatation and bradycardia. With the same objective a transient increase in cerebral vascular resistance occurs, and subsequently the resultant reflex hypotension could be responsible for correcting cerebral arteriolar vasodilatation.

On the other hand, when a lower body negative pressure is applied, a transient and partial reduction in blood pressure is induced by indirect baroreceptor stimulation. The reflex increase of sympathetic activity is small, as indicated by a slight increase in heart rate during the test. Increased cerebral vascular resistances are already present at baseline in patients and show a further increase in response to blood pressure reduction. In healthy subjects no significant changes occurred.

If is not easy to explain why patients at baseline showed higher values of cerebral vascular resistance; it is still more difficult to understand why a moderate reduction in blood pressure can induce an increase in these resistance values.

Since it was shown[14] that autonomic control of cerebral vascular resistance is tonically active, we could suppose that in patients with carotid sinus syndrome this adrenergic output is normally increased, and that moderate changes in arterial pressure are able to induce a further selective increase in its activity.

The pathophysiological substrate for these findings could be a specific cerebral vascular disease, or the expression of a more generalised atherosclerotic disease. Otherwise, it could be related to the same ''central hypersensitivity'' proposed in the genesis of carotid sinus syndrome,[10] generating abnormal adrenergic reactions toward cerebral arterioles.

UNDENIABLE ROLE OF CEREBRAL AUTOREGULATION

During tilt testing it is common to observe that some patients tolerate very low values of blood pressure without symptoms, while others experience syncope with moderate hypotension or bradycardia. In rare cases syncope also occurs in the absence of significant modifications of blood pressure and heart rate. These different pictures are probably the expression of an active contribution of cerebral autoregulation in the genesis of syncope. More difficult to understand is the mechanism triggering such an increase in cerebral vascular resistance.

The hypothesis of the presence of a significant hyperventilation before syncope, able to induce hypocapnia triggered cerebral vasoconstriction, seems to be unlikely. Hyperventilation is not always present during tilt testing before syncope and, when it occurs, it does not seem so pronounced as to justify a relevant hypocapnia, sufficient to induce loss of consciousness. However, it could play a role in making the patient more sensitive to hypotension. Similarly, it is difficult to consider that the myogenic mechanism of cerebral autoregulation could suddenly present with such paradoxical behaviour.

Therefore, if a primary role of metabolic and myogenic mechanisms in the genesis of neurally mediated syncope is difficult to support, more plausible is an involvement of autonomic activity.

Double sympathetic innervation of cerebral arterioles further complicates the interpretation of the underlying mechanism: is cerebral vasoconstriction induced by an imbalance of the two components or does it result from an altered activity of one or both pathways?

The more probable hypothesis is that cerebral autoregulation is a ''victim'' of a ''central arch'' of the same inhibitory reflex, originating from the brainstem, which induces peripheral vasodilatation and bradycardia when syncope develops.

Involvement of cerebral vasoconstriction confirms the complexity of the pathophysiology of neurally mediated syncope, and the need to adopt a comprehensive approach in the study of this problem. Other studies are needed to define the precise mechanism of the autonomic reflex involved, especially in carotid sinus syndrome, in the hope that its clarification can provide new insights into the treatment of this condition.

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IMAGES IN CARDIOLOGY

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Traumatic left ventricular true aneurysm: echocardiographic, MRI, and intraoperative images

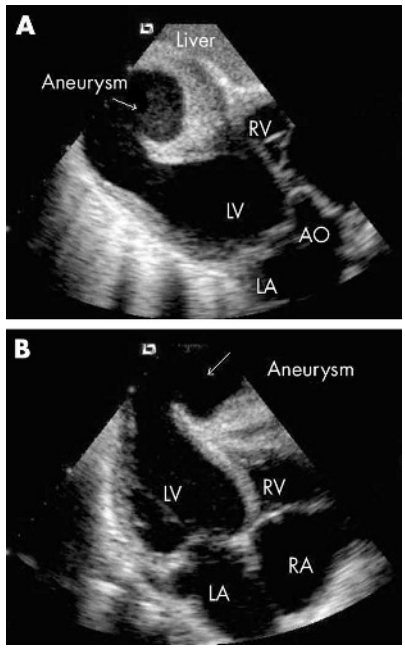
A 12 year old boy presented in Kinshasa (Democratic Republic of Congo) with chest pain and lower limb oedema, reporting a history of blunt chest trauma after falling from a tree five years ago. Examination revealed a hyperdynamic pericordial bulge, no audible murmur, and hepatomegaly.

Two dimensional transthoracic echocardiography (TTE) performed by a portable machine (Acuson-Cypress, USA) demonstrated a giant apicolateral aneurysm (9 × 7 cm), communicating with the left ventricular (LV) apex (panels A and B). Colour Doppler showed to and fro flow. The LV was dilated (5.2 cm, + 5.1 Z score), with mildly decreased function.

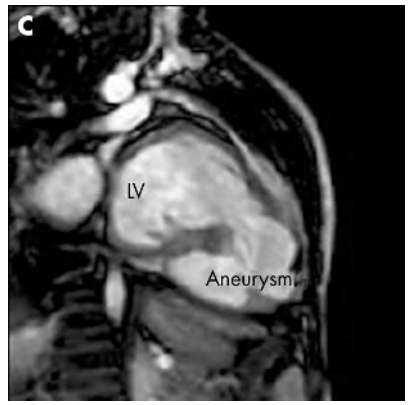
Referred to our institute by a charity organisation (Chain of hope-Belgium), TTE and ventricular angiography confirmed the diagnosis. Coronary angiography was normal. Magnetic resonance imaging (MRI) demonstrated ruptured LV apicolateral aspect, suggesting a pseudoaneurysm (panel C). After surgical excision (panel D), histopathology revealed a true aneurysm with dense connective tissue and myocardial fibres. Pathogenesis was attributed to remodelling of scarred myocardium secondary to transmyocardial contusion. Consequently, TTE and MRI proved insensitive in discriminating between true aneurysm and pseudoaneurysm.

At one year follow up in the Congo, the patient's physical examination and LV size and function were normal. Two years postoperatively, he died suddenly after an attack of convulsions a few days after a second trauma. Ventricular arrhythmia was suggested, but no post-mortem examination was performed.

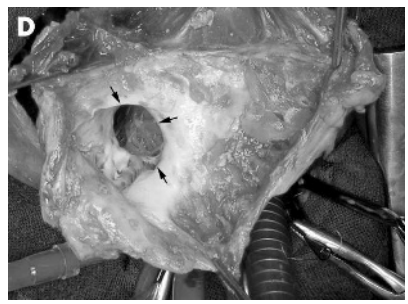
In conclusion, a true aneurysm has a diminished risk of rupture, yet affects ventricular functions. Surgical excision improves the functions, but may evoke arrhythmogenic foci, raising the need for long term antiarrhythmic management after repair of a traumatic aneurysm.



Transthoracic two dimensional echocardiography: subcostal (A) and apical four chamber view (B) demonstrating a giant apicolateral aneurysm (arrow) communicating with the left ventricular apex. AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



Magnetic resonance image, oblique view, demonstrating a giant aneurysm adjacent to the left ventricle (LV).



Surgical image of the opened aneurysm showing its communication with the left ventricular apex (arrows).

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